



IN THE UNITED STATES PATENT OFFICE

Inventor : W. Roy KNOWLES, M.D.
Filing Date: 19 July 2000
Ser. No.: 09/619,142
Art Unit: 1614
Examiner: Vickie KIM

TECH CENTER 1600/2900

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DECLARATION

- 1) I am the inventor of record for the captioned patent application. I make this declaration under 37 Code of Federal Regulations Rules 131 and 132.
- 2) Not later than March 24, 1995, I conceived of an invention having each of the elements of my pending patent claims.
- 3) The art, however, intimated that my combination would have adverse side effects, and possibly be ineffective. I thus needed to test it to assure that it was safe and effective for the claimed use.
- 4) I thus began testing on human volunteers, or "test subjects," various claimed combinations. I maintained a record of observations and results for each test subject. I enclose several records as exhibits. Note that on these records, I have redacted material private or not germane. The term "special minoxidil" is shorthand for a formulation encompassed by my pending patent claims including minoxidil. I include case studies here encompassing a variety of formulations and concentrations within the scope of the pending claims. To assure fullness of disclosure, I include case studies both successful and unsuccessful. All this testing was done in the United States of America.
- 5) Testing Protocol. The test protocol followed was generally as follows: Informed consent of the test

subject was obtained. The test subject was then given a visual demonstration of where and how much compound was to be applied. The test subject would observe the demonstration on the test subject's scalp, the test subject using a hand-held mirror to observe it. The amount of compound and locations of administration were specified until the test subject acknowledged understanding. Test subjects were instructed to telephone if they did not fully understand the instructions, or if any questions subsequently arose.

- 6) Evaluation. Test subjects were instructed to return at four-month intervals during the first year. The first visit was to determine if there might be scalp irritation. At that time, the test subject was asked to review exactly how he or she applied the test compound. Then, the entire scalp was examined using a 15-power magnifying lens, to observe if any new hairs were beginning to push through the scalp.
- 7) Usually, one could not see actual hair at four months, but could often see little black dots, which were the follicular openings beginning to enlarge prior to the hair actually beginning to show. This is analogous to seeing the ground break before a tulip pushes through the soil.
- 8) The second visit was scheduled approximately at the eight month after testing began. Compound application continued on a twice-daily basis until as much hair as could be stimulated to grow had been accomplished. This often took months, or even years, depending on factors such as the compound concentration.

- 9) Test subjects were investigated for any side effects, such as sudden weakness, feeling faint, fatigue, rapid heart beat, and sexual function or dysfunction. Any side effects were to be noted in the test record.
- 10) Results. Using this protocol, and a variety of formulation strengths, I have found several surprising things. First, testosterone blockers are not actually necessary for my invention to work; minoxidil alone is effective on 8% of patients, while the same amount of minoxidil administered with the proper amount of a penetration enhancer is effective on 35% of patients. Second, testosterone blockers added to such a mix are synergistically beneficial, increasing the efficacy from 35% to 85% of patients. As examples, I include records from several individual test subjects.
- 11) Test Subject G.J.P. Not later than June 6, 1994, I began to test my claimed invention on test subject "G.J.P." G.J.P. is a male, approximately 44 years old at the time we began testing. The redacted test record for G.J.P. is included as Exhibit G.J.P.
- 12) The record shows that for the June 6, 1994 examination, "Excellent response with minoxidil, has a small 2" area in vertex which is not fully grown over, but has much lanugo hair." I note that the test record reference to "minoxidil" refers not to minoxidil alone, but to minoxidil in admixture as described in my patent application.
- 13) The record shows that at the October 7, 1996 examination, the test subject "Has good laguno hair in the occiput. All other hair has grown out."

- 14) The record shows that at the March 1, 1999 examination, my invention ("special minoxidil," or "Spec. minox.") "is holding hair well. Front looks good. Thinning spot in occ." This finding - that the test subject was holding his hair well - was surprising, and ran counter to the conventional teaching of the art that topical minoxidil shows a 50% drop in efficacy after approximately three years of use.
- 15) Test Subject C.T. Not later than Feb. 8, 1994, I began testing a claimed compound on test subject "C.T." C.T. is a male. The redacted test record for this test subject is included as Exhibit C.T.
- 16) The test record for the Feb. 8, 1994 examination says, "He also has male pattern baldness with the yoke around the front forelock, start special minoxidil."
- 17) The record shows that at the subsequent Aug. 3, 1994 examination, "Is getting new hair growth from minoxidil, more in occiput, with some tongues of ha[ir] coming across the frontal part, good black dot formation." Black dot formation is a reference to the growth of new hairs, which appear initially as black dots on the scalp.
- 18) The record shows that at the subsequent Sept. 15, 1994 examination, "Is continuing to use special minoxidil."
- 19) The record shows that at the subsequent Aug. 3, 1995 consultation, the test subject was given a refill of special minoxidil.
- 20) The record shows that at the subsequent Jan. 29, 1996 consultation, the test subject was given a refill of special minoxidil.
- 21) Test Subject S.S. Not later than March 10, 1994, I began testing a claimed compound on test subject "S.S."

The redacted test record for S.S. is included as Exhibit S.S.

- 22) The test record for the March 10, 1994 consultation says, "Refill faxed to pharm. for special min. 1 x only." Because this record refers to a "refill" (rather than a new administration), some time before March 10, 1994, I had examined the test subject and began to test their reaction to "special minoxidil."
- 23) The record shows that at the subsequent Nov. 11, 1994 consultation, "special min w 1½ %." This indicates that the concentration of minoxidil in the mixture was changed to 1½%.
- 24) The record shows that at the subsequent Aug. 2, 1995 examination, "Hair is growing. Is using unfiltered minoxidil. Switch to filtered 1½%. Is growing good hair in occiput. Many blonde hairs present."
- 25) Test Subject E.K. On March 29, 1995, I began testing a compound within the scope of the claims on test subject "E.K." E.K., a male test subject, was 45 years old at the time we began testing. The redacted test record for E.K. is included as Exhibit E.K.
- 26) The test record for the initial (March 29, 1995) examination says, "Male pattern baldness, has used Rogaine for approx. 5 years with fair control of hair loss. Most loss is in the occiput. The baldness comes from both sides, perhaps a little more from the father. He is very willing to use special minoxidil. ... Very minimal loss in the M Peaks to use one or two drops twice daily there." Testing began using a composition including 1% minoxidil.

- 27) The record shows that at a subsequent (October 24, 1995) examination, "Minoxidil [1.0%] is producing good results at this stage. I see good black dotting across the occiput and along the existing hair on top on the parietal sides. Some early growth in front." As I mentioned earlier in this Declaration, the "black dotting" the record refers to indicates new hair growth.
- 28) The record shows that at a subsequent (December 17, 1996) examination, "Hair is growing very nicely. He looks as though he has not lost any. A lot of it is minoxidil hair. I could not point out to him with a mirror which was minoxidil vs. normal terminal hair."
- 29) The record shows that at a subsequent (April 14, 1998) examination, the test subject "thought the minoxidil solution irritated his scalp however he is using Dial soap and perhaps was using Dial shampoo. He's not sure. The area in the occiput looks more sun induced redness than a chemical from the vehicle N."
- 30) Test Subject C.G. Not later than March 18, 1994, I began testing a claimed compound on test subject "C.G." The redacted test record for this test subject is included as Exhibit C.G.
- 31) The test record for the March 18, 1994 examination says, "Ran out of minoxidil, in to have it refilled. Has begun to grow some hair around the existing hair of sides in occiput. Continue." Because the record indicates a "refill," the record shows the test had begun at some time prior to March 18, 1994.
- 32) The test record for the subsequent Nov. 29, 1995 examination says, "Has a new home and a new wife. Now wants a new head of hair. Is growing good lanugo hair."

Increase minoxidil to 1½ and continue. Good lanugo hair allover, even in longtime extensive frontal bald areas."

- 33) Adverse Drug Reactions. In all of the clinical testing I have done, I have had to stop administering test compound only on two occasions.
- 34) On one occasion, the test subject thought his heart rate had increased, although he had been in a minor car accident the day before and felt fine by the time he called me. I stopped it prophylactically because he did not want to come into the office for an inspection.
- 35) The other occasion was scalp irritation that occurred because of overuse.
- 36) Roentsch. I have read Roentsch, United States Letters Patent No. 5,654,337. Roentsch discloses and claims an improved skin penetration compound. Roentsch teaches that his new transdermal drug delivery compound delivers drugs completely through the skin and into the systemic bloodstream. Roentsch at col. 1, line 7-21, says:
- This invention relates to a composition useful in the delivery of pharmaceutically active agents through the skin. In one embodiment of the invention, the composition is formulated with a non-steroidal anti-inflammatory agent, such as ibuprofen or ketoprofen; a muscle relaxant, such as cyclobenzaprine; or other active ingredient. Such formulation is rapidly absorbed through the skin to provide local relief from pain, muscle spasms, or other pathological condition. In another embodiment of the invention, the composition is formulated with an antineoplastic or other pharmaceutically-active agent. Such formulation is rapidly absorbed through the skin to provide local delivery to subcutaneous tumors and other subdermal sites in need of treatment.
- 37) On reading this passage, one of skill in the art would understand Roentsch to teach compounds for transdermal

drug delivery - that is, delivery completely through the skin, into the tissue under the skin, and the systemic blood circulation. Delivery completely through the skin could deliver drug into muscle tissue, subcutaneous tumors, and to other sites "subdermal," that is, underneath the skin. This interpretation of Roentsch is expressly confirmed by the Roentsch reference itself (at col. 2, line 65-67).

- 38) This interpretation is also confirmed by the experimental examples expressly recited in the reference.
- 39) One such example provides for the systemic administration of nifedipine (id. at col. 3, line 59-60 and Example 7). Nifedipine is the generic name for 1,4-dihydro-2,6-dimethyl-4-(2'-nitrophenyl)-3,5-pyridine dicarboxylic acid dimethyl ester. It is pharmacologically classified as a dihydropyridine calcium channel blocker. It is sold under various tradenames (e.g., Procardia®, Nifedikor®, Duranifin® etc...). Whatever the tradename, nifedipine is indicated as a cardiac drug, for the treatment of angina pectoris (a clinical symptom due to myocardial ischemia), hypertension, or Raynaud's Phenomenon (spasms of the arterioles). As a cardiac drug, nifedipine is useful only when systemically administered - that is, when administered into the systemic blood circulation, where it can be effective against the indicated ailments. Specifically, I know of no use of nifedipine in skin tissue, nor in anything other than the systemic blood system. Because nifedipine is known only as a cardiovascular pharmaceutical for systemic administration into the systemic blood circulation, one of skill in the

art, on reading Roentsch's description of the use of nifedipine with Roentsch's skin penetration compounds, would reasonably conclude that Roentsch's skin penetration compounds make the drug penetrate completely through the skin into the systemic blood circulation.

40) Another such example provides for the systemic administration of cyclobenzaprine (see Examples 8 and 10). Cyclobenzaprine is pharmacologically classified as a skeletal muscle relaxant. As such, it is useful only when systemically administered - that is, when administered to the skeletal musculature, where it can be effective as a skeletal muscle relaxant. Because cyclobenzaprine is known only for use as a skeletal muscle relaxant, one of skill in the art, on reading Roentsch's description of the use of it with Roentsch's skin penetration compounds, would reasonably conclude that Roentsch's skin penetration compounds make the drug penetrate completely through the skin into the skeletal musculature.

41) Another such example provides for the systemic administration of aminophylline (id. at col. 3, line 59-60 and Example 13). Aminophylline is the generic name for 3,7-dihydro-1,3-dimethyl-1H-purine-2,6-dione in a 2:1 compound with 1,2-ethanediamine. It is pharmacologically classified as a bronchodilator and a veterinary bronchodilator. It is sold under various tradenames (e.g., Cardophyllin®, Pulmovet®, etc...). Whatever the tradename, aminophylline is indicated as a bronchodilator (Phyllotemp®); for the treatment of bronchospasm in asthma, emphysema or chronic bronchitis (Phyllocontin®); asthma (Afonilum®); or cough (Pecram®). As such, it is

useful only when systemically administered - that is, when administered into the systemic blood circulation, where it can be effective against the indicated ailments.

- 42) Aminophylline is a central nervous system stimulant; as such, its known side effects include restlessness, anorexia, nausea, and dehydration. CNS stimulants are the mainstay of the over the counter diet pill industry, and Roentsch discusses the use of aminophylline as such (to reduce cellulite). Roentsch confirms that such usefulness requires aminophylline to penetrate completely through the skin into the musculature and adipose tissue (Roentsch specifically notes his claimed penetration enhancer delivers drug completely through the skin and into the sub-dermal adipose tissue. Id. at col. 10, line 39.) Aminophylline has no known use in skin tissue. Because aminophylline is known only for use as a systemic drug (bronchodilator or CNS stimulant), one of skill in the art, on reading Roentsch's description of the use of aminophylline with Roentsch's skin penetration compounds, would reasonably conclude that Roentsch's skin penetration compounds make the drug penetrate completely through the skin into the systemic blood circulation.
- 43) Roentsch confirms this teaching consistently in his patent. He mentions, for example, inclusion of bacitracin or another antibiotic - but takes pains to specify that his penetration enhancer would help the antibiotic penetrate not into infected skin, but completely through the skin, "to sites of infection induced by puncture wounds." Id. at col. 6 line 21-26. Puncture wounds are, by definition, wounds which puncture

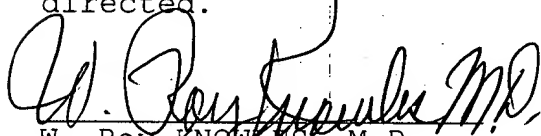
completely through the skin and into the underlying musculature and adipose tissue.

44) Roentsch also says, "compositions comprising a mixture of minoxidil and a testosterone 5 α -reductase inhibitor would be very beneficial for inducing hair growth." Id. at col. 6 line 15-16. Roentsch, however, acknowledges that his skin penetration enhancer has "very good skin penetration," id., and thus cautions that his compound be used only "as long as local reactions or toxicity due to the active ingredient do not become a problem," id. at lines 36-40.

45) Roentsch thus does not suggest nor enable a way to avoid systemic toxicity and side effects due to systemic administration of minoxidil or 5 α -reductase inhibitor. To the contrary, by teaching a highly effective skin penetrant, Roentsch teaches the person of skill in the art to avoid using his (or any other) skin penetrant with minoxidil or 5 α -reductase inhibitor, unless that person also has a mechanism to prevent "local reactions or toxicity due to the active ingredient." Roentsch fails to teach or suggest any such mechanism. Roentsch thus (a) actively dissuades practicing, or "teaches away from," my claimed invention, and (b) fails to enable one of skill to practice the claim limitation, "*penetrating the skin surface to a depth of approximately the depth of hair bulbs.*" I have reviewed each of the several dozen patent and non-patent references now of record. None of these references contain any factual showing that Roentsch enables the claim limitation "*penetrating the skin surface to a depth of approximately the depth of hair bulbs.*"

46) I understand that the latest office action makes a factual assertion that "One of skilled artisan would have envisaged the enhanced delivery of active compound to the hair bulbs . . . via improved penetration thru skin layers by penetration enhancer." OFFICE ACTION at 4 (24 April 2002). That factual assertion is incorrect. I envisaged this solution - not Mr. Roentsch.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United State Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon or any patent to which this verified statement is directed.


W. Roy KNOWLES, M.D.
June 24, 2002

X:\Shared Documents\knowles\R131 Decl v.3

Rule 1.131 Declaration
Inventor: KNOWLES, W.R.
Filing Date: 19 July 2000
Ser. No.: 09/619,142

EXHIBIT J.P.G.



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TECH CENTER 160012900

NAME [REDACTED] AGE [REDACTED] DATE 9-10-90 DR. [REDACTED]
END BILL TO [REDACTED] ADDRESS Houston, Texas 77062 PHONE [REDACTED]
EMPLOYED BY [REDACTED] REFERRED [REDACTED]
INSURANCE [REDACTED] DRIVER'S LICENSE # [REDACTED]

06-06-94 Excellent result with minoxidil, has a small 2" area in vertex which is not fully grown over, but has much lanugo hair. Continue. Recheck in one year or so.

4-6-95 Refill of min. 1% filtered Oled to pharm prn. *OK*
3-8-95 Refill of min. 1% filtered Oled to pharm prn. *OK*

0-07-96 Has been out of Minoxidil for approximately one week. Has good lanugo hair in the occiput. All other hair has grown out. Refill prn for 1% filtered. Advised that this would be stronger than what he has been using.

1-29-98 Pt. had been unhappy in pharm where he gets minox. Would like to start back on it. Pres. faxed to Lifecheck. *OK*

3-01-99 Spec. minox. is holding hair well. Front looks good. Thinning spot in occ. Cont. spl. minox. Given 1 btl.

1-29-98 Pt. had been unhappy in pharm where he gets minox. Would like to start back on it. Pres. faxed to Lifecheck. *OK*

Rule 1.131 Declaration
Inventor: KNOWLES, W.R.
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EXHIBIT C.T.

C.T.

SEND BILL TO

ADDRESS Houston, TX 77005

PHONE

EMPLOYED BY

W:

REFERRED

INS:

ALLERGY: POSSIBLY PENICILLIN

02-08-94

[REDACTED]

He also has male pattern baldness with the yoke around the front forehead, start special minoxidil.

08-03-94

Is getting now hair growth from minoxidil, more in occiput, with some tongues of hair coming across the frontal part, good black dot formation, this was explained to pt. Also, seborrhea, he is under some pressure at work. 40 KIM lt. JH. Continue Minoxidil, he has definitely been over using this, using a bottle every 3 weeks, reeducated in proper amount.

09-15-94

Under intense pressure with law practice, making all kinds deals, meeting deadlines etc. Is continuing to use special minoxidil. Daughter comments on how much flaking and redness he has, he admits that he is under intense stress. 40 KIM rt. JH. Kenalog spray sparingly.

8-3-95 Phone call to Pharm. Switch Minoxidil to
1-29-96 Refill for minox 1 1/2 fl oz / 1 oz by JH

Rule 1.131 Declaration
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EXHIBIT S.S.

SEND BILL TO

ADDRESS Houston, Texas 77062

PHONE

EMPLOYED BY

REFERRED

ALLERGIC TO:

Penicillin

INSURANCE

DRIVER'S LICENSE #

3-10-94 Refill OKed to Pharm. for special Min. 1/2 only
11-11-94 Pharm called, WKK O'Ked special min w 1 1/2 of
with 2 refills - to Ken's -
8-1-95 Needs to be seen for refil of minox. JH

8/2/95 Hair is growing. Is using unfiltered minoxidil. Switch to filtered 1 1/2%. Is growing good hair in occiput. Many blonde hairs present. Some of them in the occiput only 1/8 of an inch or less in length. Is probably rubbing them off although he denies this.

9-11-96 Refill Minox 1 x only. JH

02-18-97 Ran out of Special Minoxidil one week ago. Refill 1-1/2% filtered. [REDACTED]

09/15/98 Had 2 bottles of minoxidil [REDACTED] in January. Has recently run out. [REDACTED] Will have to come her for refills. Loss is present only in occiput. JH

Rule 1.131 Declaration
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EXHIBIT E.K.

EMPLOYED BY

REFERRED WIFE

INSURANCE

DRIVER'S LICENSE #

03/29/95 Male pattern baldness, has used Rogaine for approx. 5 years with fair control of the loss. Most loss is in the occiput. The baldness comes from both sides, perhaps a little more from the father. He is very willing to use special Minoxidil 1% foam was called into Briargrove. He will check with us in 6 months. I expect and to him so that he will get an excellent response. Very minimal loss in the M Peaks to use one or two drops twice daily there.

10-6-95 Refill Ok'd to Pharm. [redacted] for
Special minox 1% H

10/24/95 Minoxidil is producing good results at this stage. I see good black dotting across the occiput and along the existing hair on top on the parietal sides. Some early growth in front. Continue minoxidil, 1% filtered. Recheck in 6 months.

7-10-96 Minox. refill ok'd to Pharm [redacted] for
12/17/96 Hair is growing very nicely. He looks as though he has not lost any. A lot of is minoxidil hair. I could not point out to him with a mirror which was minoxidil vs. normal terminal hair. Continue special minoxidil.

04/14/98

[redacted] Thought the minoxidil solution irritated his scalp however he is using Dial soap and perhaps was using Dial shampoo. He's not sure. The area in the occiput looks more sun induced redness than a chemical from the vehicle N.

Rule 1.131 Declaration
Inventor: KNOWLES, W.R.
Filing Date: 19 July 2000
Ser. No.: 09/619,142

EXHIBIT C.G.

SEND JUL 10

ADDRESS Houston, Texas 77043--

PHONE

EMPLOYED BY

REFERRED

C.G.

INSURANCE

DRIVER'S LICENSE #

05-18-94 Ran out of minoxidil, in to have it refilled. Has begun to grow some hair around the existing hair of sides in occiput. Continue, recheck as needed.

11/29/95 Has a new home and a new wife. Now wants a new head of hair. Is growing good lanugo hair. Increase minoxidil to 1 1/2% and continue. Good lanugo hair all over, even in longtime extensive frontal bald areas. Check in 6 months.

1-20-97 Pt. had appt. 12-26 which he missed, he then had an appt. this AM at 8:15 but Dr. K. was not in the office, we tried to call pt. but numbers not correct. Pt. made another appt. for Feb. I called in to Pharm. I refilled only of Special Minnox. II